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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/577,343	03/05/2007	Yasuharu Nishimura	P29875	4864

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EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	**PAPER NUMBER**
1643	

NOTIFICATION DATE	DELIVERY MODE
10/17/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/577,343	NISHIMURA ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) *1 and 2* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/13/07 and 11/30/07* .
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-7 are all the pending claims in this application.

Election/Restrictions

2. Applicant's election with traverse of Group II (Claims 3-7) in the reply filed on 7/17/08 is acknowledged. The traversal is on the ground(s) that under 37 CFR 1.475 a 371 application has unity of invention if the claims are drawn to a process and an apparatus or means of performing the process, and that the examiner's reliance on the Nakatsura reference to establish that the prior art teaches the special technical feature of the invention is improper because Nakatsura is published after the priority filing date for the Japanese language priority document.

Applicant's arguments have been carefully considered but are not deemed persuasive for the following reasons:

For an application filed under PCT 371, a requirement for restriction is proper when an application relates to more than one inventions and said inventions are not linked under a single inventive concept; then there is lack unity of invention (PCT Rule 13.1). According to Rule 13.2, unity of invention exists only in cases where the technical relationship among the claimed inventions involves a corresponding special technical feature. The term "special technical feature" is referred to as the technical feature that defines a contribution that each of the inventions, considered as a whole, makes over the prior art (Rule 13.2). Whether or not any particular technical feature makes a "contribution" over the prior art, and therefore constitutes a "special technical feature," is

considered with respect to novelty and an inventive step. A lack of unity occurs when the technical feature linking the different invention groups is not special or when there are multiple technical features.

Further, Applicants have not provided a certified translation of their Japanese priority document to perfect their priority claims and to antedate the Nakatsura reference.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 1 and 2 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 7/17/08.

4. Claims 3-7 are all the pending claims under examination.

Information Disclosure Statement

5. The U.S. and foreign patent references and the non-patent literature references cited in the IDS' of 11/13/07 and 11/30/07 have been considered. The English language Abstracts for the Japanese language documents cited in the IDS of 11/13/07 have been stricken because the source of the translation and the date of translation are not cited on the 1449 form. The Nakatsura et al. reference cited in the PTO 892 form of 6/17/08 has been stricken on the IDS of 11/30/07. The information is cumulative under 37 CFR 1.56(b). A copy of the 1449 forms from the 11/13/07 and 11/30/07 IDS is attached hereto.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claim 6 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example Ex parte Dunki, 153 USPQ 678 (Bd. App. 1967) and Clinical Products Ltd. v. Brenner, 255 F Supp. 131,149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

7. Claims 3-7 are rejected under 35 U.S.C. 102(a) as being anticipated by Nakatsura et al. (Clin. Can. Res. 10:6612-6621 (10/1/2004); cited in the PTO 892 form of PTO 892 form of 6/17/08).

Claims 3-5 and 7 are interpreted as being drawn to a method for diagnosing a melanoma comprising detecting or measuring GPC3 in a sample (Claim 3), where the sample of Claim 3 is contacted with an anti-GPC3 antibody (Claim 4), or where the method of Claim 3 comprises quantifying GPC3 in a sample (Claim 5), or where the

method of Claim 4 comprises quantifying GPC3 in a sample (Claim 7). Claim 6 is interpreted as being drawn to a method using GPC3 as a tumor marker for malignant melanoma where the term “use” is interpreted as meaning detecting.

Nakatsura describe methods where glypican-3 is used as a melanoma cancer marker and describe antibodies, primers and probes for detecting melanomas (Methods and Materials, p. 6613, Col. 1, ¶3 and 4).

Nakatsura teaches detection of GPC3 mRNA in human melanoma cell lines (Figure 1A).

Nakatsura teaches detection of GPC3 by immunohistology in melanoma tissues (Table 1 and Figure 2).

Nakatsura teaches quantitation and detection by ELISA method of GPC3 protein in sera from 91 preoperative melanoma patients, 5 patients with large congenital melanocytic nevus, and 60 healthy donors (Fig. 3B and Table 1).

Nakatsura describe diagnosing 40% of patients irrespective of clinical stages by using serum glypican-3 as a tumor marker. Nakatsura states “GPC3 protein in the sera was detectable in patients with melanoma, but not in disease-free patients after removal of the primary lesion or patients with large congenital melanocylic nevus and healthy donors, thus indicating the specificity of serum GPC3 to be 100% except for patients with hepatocellular carcinoma who were also positive for serum GPC3”…”We confirmed the disappearance of GPC3 protein in of 11 patients after surgical treatments for melanoma. Thus GPC3 is useful for monitoring the response to treatment. Taken

together, these results indicate that GPC3 may prove to be an appropriate candidate for use in making a diagnosis for numbers of patients with melanoma" (p. 6618, Col. 2, ¶2).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. Claims 3-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Katagiri et al. (20030165954; published 9/4/03; filed January 9, 2003) in view of Desai et al. (J. Med. Genet. 35:476-481 (1998)) as evidenced by Nakatsura et al. (Clin. Can. Res. 10:6612-6621 (10/1/2004); cited in the PTO 892 form of PTO 892 form of 6/17/08).

The interpretation of Claims 3-7 is discussed above under section 7.

The diagnostic method was prima facie obvious at the time of the invention over Katagiri in view Desai as evidenced by Nakatsura.

Katagiri discloses detecting the level of expression of one or more drug sensitivity genes such as GPC3 comprises detecting the level of mRNA expressed from the drug sensitivity genes, detecting the level of mRNA expressed from the drug sensitivity genes comprises exposing the mRNA to a nucleic acid probe complementary to the mRNA or performing an INVADER assay, or detecting the level of polypeptide expressed from the drug sensitivity genes comprises exposing the polypeptide to an antibody specific to the polypeptide and detecting the binding of the antibody to the polypeptide [0005]. Katgiri teaches methods for detection of expression of cancer markers (e.g., to determine drug sensitivity scores or drug sensitivity profiles) where expression is measured directly (e.g., at the RNA or protein level), in tissue samples (e.g., biopsy tissue), or in bodily fluids (e.g., including but not limited to, plasma, serum, whole blood, mucus, and urine) [0096]. Katagiri teaches gene expression of cancer markers is detected by measuring the expression of the corresponding protein or polypeptide, for example, GPC3, by any suitable method including immunohistochemistry methods or binding to an antibody raised against the protein (e.g., radioimmunoassay, ELISA (enzyme-linked immunosorbant assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitation reactions, immunodiffusion assays, in situ immunoassays (e.g., using colloidal gold, enzyme or radioisotope labels, for example), Western blots, precipitation reactions, agglutination assays (e.g., gel agglutination assays, hemagglutination assays, etc.), complement fixation assays, immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc.) [0104-0105]. Katagiri teaches the antibody/antigen

can be detected with matrixes, complexes can be dissociated from the matrix, and the level of cancer markers binding or activity determined using standard techniques. Other techniques for immobilizing either cancer markers protein or a target molecule on matrices include using conjugation of biotin and streptavidin. [0162] Katagiri teaches and appreciates GPC3 is a drug sensitive gene and diagnosing GPC3-expressing cancers with diagnostic and quantitative methods but does not specifically disclose that GPC3 expression is associated with skin cancers such as melanoma whereas Desai as evidenced by Nakatsura does.

Desai teaches that a subset of a juvenile polyposis (JP) patient population was found to have dermatological abnormalities including telangiectases and large numbers of pigmented naevi. Increased number of pigmented naevi common followed by including telangiectasia of the skin and mucous membranes, cutaneous and subcutaneous swellings, and skin pits. One patient had a basal cell carcinoma (p. 477, Col. 2, ¶5). Desai teaches that one patient, patient 18, had features consistent with Simpson-Golabi-Behmel (SGB) syndrome, and although “juvenile polyps are not documented as a regular feature of this condition, it is well known to show very variable penetrance, and since macrocephaly and hypertelorism are common features in our cases, it does beg the question as to whether the male excess of cases of JP in our series could be the result of X linked conditions. Mutations in the glypican gene, GPC3, have been found to underly SGB syndrome and should allow us to test for germline mutations in this cohort" (p. 479, Col. 2, ¶1).

As evidenced by Nakatsura, GPC3 gene expression is shown to be inherent

characteristic in a skin abnormality such as melanoma. Nakatsura is effective as art to show inherency for the melanoma expression of GPC3 pursuant to MPEP 2131.01:

> ""III. To show that a characteristic not disclosed in the reference is inherent"...Note that as long as there is evidence of record establishing inherency, failure of those skilled in the art to contemporaneously recognize an inherent property, function or ingredient of a prior art reference does not preclude a finding of anticipation. *Atlas Powder Co. v. IRECO, Inc.* 190 F3d 1342, 1349, 51 USPQ2d 1943, 1948 (Fed. Cir. 1999)...Also note that the critical date of extrinsic evidence showing a universal fact *need not antedate* the filing date (MPEP 2124)."

Under the recent KSR decision, the cited references of art are not required to "*explicitly* teach or suggest" all of the steps or elements of a method. The Supreme Court has determined in *KSR International Co. v. Teleflex, Inc.*, 550 U.S._, 82, USPQ2d 1385 (2007), that "a person of ordinary skill attempting to solve a problem will" not " be led only to those elements of prior art designed to solve the same problem....." (KSR, 550 U.S. at_, 82 USPQ2d at 1397). In addition, the court found that "When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variant, 35 USC 103 likely bars its patentability" (KSR, 550 U.S. at_, 82 USPQ2d at 1396). Further the court found that the Federal Circuit has erred in applying the teaching-suggestion-motivation test in an overly rigid and formalistic way, in particular by concluding "that a patent claim cannot be proved

obvious merely by showing that the combination of elements was 'obvious to try'" (KSR, 550 U.S. at_, 82 USPQ2d at 1397) and has further determined that "…….[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results" (KSR, 550 U.S. at_, 82 USPQ2d at 1395). The court further found that "…… the conclusion that when a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious" (KSR, 550 U.S. at_, 82 USPQ2d at 1395-1396). Thus, when considering obviousness of a combination of known elements, the operative question is "whether the improvement is more than the predictable use of prior art elements according to their established functions" ((KSR, 550 U.S. at_, 82 USPQ2d at 1396).

The ordinary artisan would have been motivated and been assured of reasonable success in having produced the diagnostic method at the time of the invention based on Katagiri in view of Desai as evidenced by Nakatsura. Katagiri and Desai teach expression of GCP3 in hyperproliferative disorders and cancer. Katagiri teaches that detecting and quantitating GCP3 is beneficial in the diagnosis of cancers because the gene is a drug-responsive gene and Katagiri teaches different methods for detecting and quantitating gene or protein expression and using antibodies to detect and quantitate the expressed protein. Desai provides motivation to consider GCP3 expression as being correlative for disorders falling within juvenile polyposis which present with dermatological abnormalities including skin cancers and increased numbers of pigmented nevei, and where as evidenced by Nakatsura, GCP3 is

inherently expressed by the skin cancer, melanoma. Because Desai expressly teaches that GCP3 may be related to a class of skin-related disorders and Katagiri teaches diagnostic methods and diagnostic criteria for detecting GCP3, and GCP3 expression is inherent to melanomas as evidenced by Nakatsura, the ordinary artisan would have been motivated to identify a tumor marker for skin-related cancers especially melanoma and more especially for a gene like GCP3 which as taught by Katagiri was not only a tumor marker but an important drug responsive element in the treatment. The ordinary artisan would have been reasonably assured of success in having produced the method based on the combined disclosure because Katagiri taught the reagents and method assays to perform such diagnostic steps for detecting GCP3 gene and protein expression, where Desai provided correlative relation between skin-related cancers or disorders and GCP3 expression levels, and finally that GPDC3 expression is inherent to the melanoma skin cancer as evidenced by Nakatsura. For all of the foregoing reasons, the claimed method was prima facie obvious at the time of the invention over Katagiri in view Desai as evidenced by Nakatsura.

Conclusion

9. No claims are allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNN BRISTOL whose telephone number is (571)272-6883. The examiner can normally be reached on 8:00-4:30, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LAB

/David J Blanchard/
Primary Examiner, Art Unit 1643